

## CLAIMS

What is claimed is:

- 1           1. A method for determining the free energy of binding of a potential ligand to a  
2    receptor, comprising the steps of:
  - 3           obtaining, for each of two or more actual receptor ligands, at least one of a structure  
4    and a free energy of binding to said receptor, such that each of said two or more actual  
5    receptor ligands has a known structure and a known free energy of binding to said receptor;  
6           orienting said structures of said two or more actual receptor ligands for maximum  
7    geometric coincidence with each other;  
8           determining an electrostatic potential at each of more than one point on a van der  
9    Waals surface of each of said actual receptor ligands;  
10          thereafter, mapping each of said electrostatic potentials of each of said actual  
11    receptor ligands onto a geometric surface of one of said two or more actual receptor  
12    ligands, each of said two or more actual receptor ligands being thereby described by an  
13    identical surface geometry but a different electrostatic potential surface, and each of said  
14    electrostatic potentials being described by positional information relating said electrostatic  
15    potentials to said geometric surface;  
16          thereafter, inputting said electrostatic potentials, said positional information, and  
17    said known free energy of binding of one of said two or more actual receptor ligands into  
18    a neural network;  
19          thereafter, training said neural network until said neural network predicts said free  
20    energy of binding of said one of said two or more actual receptor ligands;  
21          repeating said steps of inputting and training for each of the remaining said two or  
22    more actual receptor ligands to produce a trained network;  
23          thereafter, determining a potential ligand electrostatic potential at each of more than  
24    one point on a van der Waals surface of said potential ligand, said potential ligand having  
25    a known structure and an unknown free energy of binding to said receptor;

26 orienting said structure of said potential ligand for maximum geometric coincidence  
 27 with said structures of said two or more actual receptor ligands;

28 thereafter, mapping each of said electrostatic potentials of said potential ligand onto  
 29 a geometric surface of one of said two or more actual receptor ligands, said potential ligand  
 30 having a surface geometry identical to that of said two or more actual receptor ligands, but  
 31 a different electrostatic potential surface, and each of said electrostatic potentials of said  
 32 potential ligand being described by positional information relating said electrostatic  
 33 potentials to said geometric surface;

34 thereafter, inputting said electrostatic potentials and said positional information of  
 35 said electrostatic potentials of said potential ligand into said trained network; and

36 using said trained network to calculate a free energy of binding of said potential  
 37 ligand to said receptor.

1 2. A method for determining the free energy of binding of a potential ligand to a  
 2 receptor, comprising the steps of:

3 obtaining a structure for said potential ligand;

4 orienting structures of two or more actual receptor ligands for said receptor for  
 5 maximum geometric coincidence with each other;

6 each of said two or more actual receptor ligands having a known structure and a  
 7 known free energy of binding to said receptor;

8 determining an electrostatic potential at each of more than one point on a van der  
 9 Waals surface of each of said actual receptor ligands;

10 thereafter, mapping each of said electrostatic potentials of each of said actual  
 11 receptor ligands onto a geometric surface of one of said two or more actual receptor  
 12 ligands, each of said two or more actual receptor ligands being thereby described by an  
 13 identical surface geometry but a different electrostatic potential surface, and each of said  
 14 electrostatic potentials being described by positional information relating said electrostatic  
 15 potentials to said geometric surface;

16           thereafter, inputting said electrostatic potentials, said positional information, and  
 17   said known free energy of binding of one of said two or more actual receptor ligands into  
 18   a neural network;  
 19           thereafter, training said neural network until said neural network predicts said free  
 20   energy of binding of said one of said two or more actual receptor ligands;  
 21           repeating said steps of inputting and training for each of the remaining said two or  
 22   more actual receptor ligands to produce a trained network;  
 23           thereafter, determining an potential ligand electrostatic potential at each of more  
 24   than one point on a van der Waals surface of said potential ligand, said potential ligand  
 25   having an unknown free energy of binding to said receptor;  
 26           orienting said structure of said potential ligand for maximum geometric coincidence  
 27   with said structures of said two or more actual receptor ligands;  
 28           thereafter, mapping each of said electrostatic potentials of said potential ligand onto  
 29   a geometric surface of one of said two or more actual receptor ligands, said potential ligand  
 30   having a surface geometry identical to that of said two or more actual receptor ligands, but  
 31   a different electrostatic potential surface, and each of said electrostatic potentials of said  
 32   potential ligand being described by positional information relating said electrostatic  
 33   potentials to said geometric surface;  
 34           thereafter, inputting said electrostatic potentials and said positional information of  
 35   said electrostatic potentials of said potential ligand into said trained network; and  
 36           using said trained network to calculate a free energy of binding of said potential  
 37   ligand to said receptor.  
 1           3. A computer readable medium, comprising:  
 2           computer-readable information;  
 3           said information capable of interacting with a computer to produce an output;  
 4           said output being a calculated free energy of binding of a potential ligand to a  
 5   receptor;  
 6           said output being calculated by:

7           orienting structures of said two or more actual receptor ligands for  
8           maximum geometric coincidence with each other;  
9           each of said two or more actual receptor ligands having a known structure  
10          and a known free energy of binding to said receptor;  
11          determining an electrostatic potential at each of more than one point on a  
12          van der Waals surface of each of said actual receptor ligands;  
13          thereafter, mapping each of said electrostatic potentials of each of said  
14          actual receptor ligands onto a geometric surface of one of said two or more actual  
15          receptor ligands, each of said two or more actual receptor ligands being thereby  
16          described by an identical surface geometry but a different electrostatic potential  
17          surface, and each of said electrostatic potentials being described by positional  
18          information relating said electrostatic potentials to said geometric surface;  
19          thereafter, inputting said electrostatic potentials, said positional information,  
20          and said known free energy of binding of one of said two or more actual receptor  
21          ligands into a neural network;  
22          thereafter, training said neural network until said neural network predicts  
23          said free energy of binding of said one of said two or more actual receptor ligands;  
24          repeating said steps of inputting and training for each of the remaining said  
25          two or more actual receptor ligands to produce a trained network;  
26          thereafter, determining an potential ligand electrostatic potential at each of  
27          more than one point on a van der Waals surface of said potential ligand, said  
28          potential ligand having a known structure and an unknown free energy of binding  
29          to said receptor;  
30          orienting said structure of said potential ligand for maximum geometric  
31          coincidence with said structures of said two or more actual receptor ligands;  
32          thereafter, mapping each of said electrostatic potentials of said potential  
33          ligand onto a geometric surface of one of said two or more actual receptor ligands,  
34          said potential ligand having a surface geometry identical to that of said two or more  
35          actual receptor ligands, but a different electrostatic potential surface, and each of

36 said electrostatic potentials of said potential ligand being described by positional  
37 information relating said electrostatic potentials to said geometric surface;  
38 thereafter, inputting said electrostatic potentials and said positional  
39 information of said electrostatic potentials of said potential ligand into said trained  
40 network; and  
41 using said trained network to calculate a free energy of binding of said  
42 potential ligand to said receptor.

1 4. A method for determining a free energy of binding of a potential transition-state  
2 inhibitor to an enzyme, comprising the steps of:  
3 obtaining, for each of two or more enzyme substrates or inhibitors, at least one of  
4 a structure and a free energy of binding to said enzyme, such that each of said two or more  
5 enzyme substrates or inhibitors has a known structure and a known free energy of binding  
6 to said enzyme;  
7 orienting said structures of said two or more enzyme substrates or inhibitors for  
8 maximum geometric coincidence with each other;  
9 determining an electrostatic potential at each of more than one point on a van der  
10 Waals surface of each of said enzyme substrates or inhibitors;  
11 thereafter, mapping each of said electrostatic potentials of each of said enzyme  
12 substrates or inhibitors onto a geometric surface of a transition state inhibitor, each of said  
13 enzyme substrates or inhibitors being thereby described by an identical surface geometry  
14 but a different electrostatic potential surface, and each of said electrostatic potentials being  
15 described by positional information relating said electrostatic potentials to said geometric  
16 surface of said transition state inhibitor;  
17 thereafter, inputting said electrostatic potentials, said positional information, and  
18 said known free energy of binding of one of said two or more enzyme substrates or  
19 inhibitors into a neural network;  
20 thereafter, training said neural network until said neural network predicts said free  
21 energy of binding of said one of said two or more enzyme substrates or inhibitors;

22 repeating said steps of inputting and training for each of the remaining said two or  
 23 more enzyme substrates or inhibitors to produce a trained network;

24 thereafter, determining an potential transition electrostatic potential at each of more  
 25 than one point on a van der Waals surface of said potential transition-state inhibitor, said  
 26 potential transition-state inhibitor having a known structure and an unknown free energy  
 27 of binding to said enzyme;

28 orienting said structure of said potential transition-state inhibitor for maximum  
 29 geometric coincidence with said structures of said two or more enzyme substrates or  
 30 inhibitors;

31 thereafter, mapping each of said electrostatic potentials of said potential transition-  
 32 state inhibitor onto a geometric surface of one of said two or more two or more enzyme  
 33 substrates or inhibitors, such that said potential transition-state inhibitor has a surface  
 34 geometry identical to that of said two or more actual receptor transition-state inhibitors, but  
 35 a different electrostatic potential surface, and each of said electrostatic potentials of said  
 36 potential transition-state inhibitor is described by positional information relating said  
 37 electrostatic potentials to said geometric surface of said two or more enzyme substrates or  
 38 inhibitors;

39 thereafter, inputting said electrostatic potentials and said positional information of  
 40 said electrostatic potentials of said potential transition-state inhibitor into said trained  
 41 network; and

42 using said trained network to calculate a free energy of binding of said potential  
 43 transition-state inhibitor to said enzyme.

1 5. A method for determining the free energy of binding of a potential transition-  
 2 state inhibitor to a enzyme, comprising the steps of:

3 obtaining a structure for said potential transition-state inhibitor;

4 orienting structures of two or more enzyme substrates or inhibitors for said enzyme  
 5 for maximum geometric coincidence with each other;

6 each of said two or more enzyme substrates or inhibitors having a known structure  
 7 and a known free energy of binding to said enzyme;

8           determining an electrostatic potential at each of more than one point on a van der  
9    Waals surface of each of said enzyme substrates or inhibitors;  
10           thereafter, mapping each of said electrostatic potentials of each of said enzyme  
11    substrates or inhibitors onto a geometric surface of one of said two or more enzyme  
12    substrates or inhibitors, each of said two or more enzyme substrates or inhibitors being  
13    thereby described by an identical surface geometry but a different electrostatic potential  
14    surface, and each of said electrostatic potentials being described by positional information  
15    relating said electrostatic potentials to said geometric surface;  
16           thereafter, inputting said electrostatic potentials, said positional information, and  
17    said known free energy of binding of one of said two or more enzyme substrates or  
18    inhibitors into a neural network;  
19           thereafter, training said neural network until said neural network predicts said free  
20    energy of binding of said one of said two or more enzyme substrates or inhibitors;  
21           repeating said steps of inputting and training for each of the remaining said two or  
22    more enzyme substrates or inhibitors to produce a trained network;  
23           thereafter, determining an potential transition-state inhibitor electrostatic potential  
24    at each of more than one point on a van der Waals surface of said potential transition-state  
25    inhibitor, said potential transition-state inhibitor having an unknown free energy of binding  
26    to said enzyme;  
27           orienting said structure of said potential transition-state inhibitor for maximum  
28    geometric coincidence with said structures of said two or more enzyme substrates or  
29    inhibitors;  
30           thereafter, mapping each of said electrostatic potentials of said potential transition-  
31    state inhibitor onto a geometric surface of one of said two or more enzyme substrates or  
32    inhibitors, said potential transition-state inhibitor having a surface geometry identical to  
33    that of said two or more enzyme substrates or inhibitors, but a different electrostatic  
34    potential surface, and each of said electrostatic potentials of said potential transition-state  
35    inhibitor being described by positional information relating said electrostatic potentials to  
36    said geometric surface;

37           thereafter, inputting said electrostatic potentials and said positional information of  
38 said electrostatic potentials of said potential transition-state inhibitor into said trained  
39 network; and

40           using said trained network to calculate a free energy of binding of said potential  
41 transition-state inhibitor to said enzyme.

- 1           6. A computer readable medium, comprising:
  - 2           computer-readable information;
  - 3           said information capable of interacting with a computer to produce an output;
  - 4           said output being a calculated free energy of binding of a potential transition-state  
- 5 inhibitor to a enzyme;
  - 6           said output being calculated by:
    - 7           orienting structures of said two or more actual receptor ligands for  
8           maximum geometric coincidence with each other;
    - 9           each of said two or more actual ligands having a known structure and a  
10          known free energy of binding to said enzyme;
    - 11          determining an electrostatic potential at each of more than one point on a  
12          van der Waals surface of each of said enzyme substrates or inhibitors;
    - 13          thereafter, mapping each of said electrostatic potentials of each of said  
14          enzyme substrates or inhibitors onto a geometric surface of one of said two or more  
15          enzyme substrates or inhibitors, each of said two or more enzyme substrates or  
16          inhibitors being thereby described by an identical surface geometry but a different  
17          electrostatic potential surface, and each of said electrostatic potentials being  
18          described by positional information relating said electrostatic potentials to said  
19          geometric surface;
    - 20          thereafter, inputting said electrostatic potentials, said positional information,  
21          and said known free energy of binding of one of said two or more enzyme  
22          substrates or inhibitors into a neural network;



23 thereafter, training said neural network until said neural network predicts  
 24 said free energy of binding of said one of said two or more enzyme substrates or  
 25 inhibitors;

26 repeating said steps of inputting and training for each of the remaining said  
 27 two or more enzyme substrates or inhibitors to produce a trained network;

28 thereafter, determining an potential transition-state inhibitor electrostatic  
 29 potential at each of more than one point on a van der Waals surface of said potential  
 30 receptor ligand, said potential receptor ligand having a known structure and an  
 31 unknown free energy of binding to said enzyme;

32 orienting said structure of said potential transition-state inhibitor for  
 33 maximum geometric coincidence with said structures of said two or more enzyme  
 34 substrates or inhibitors;

35 thereafter, mapping each of said electrostatic potentials of said potential  
 36 transition-state inhibitor onto a geometric surface of one of said two or more  
 37 enzyme substrates or inhibitors, said potential transition-state inhibitor having a  
 38 surface geometry identical to that of said two or more enzyme substrates or  
 39 inhibitors, but a different electrostatic potential surface, and each of said  
 40 electrostatic potentials of said potential transition-state inhibitor being described by  
 41 positional information relating said electrostatic potentials to said geometric  
 42 surface;

43 thereafter, inputting said electrostatic potentials and said positional  
 44 information of said electrostatic potentials of said potential transition-state inhibitor  
 45 into said trained network; and

46 using said trained network to calculate a free energy of binding of said  
 47 potential transition-state inhibitor to said enzyme.

1 7. A method for determining the free energy of binding of a potential ligand to a  
 2 receptor according to claim 1, wherein said neural network is a feed forward network with  
 3 back propagation of error that learns with momentum.

1           8. A method for determining the free energy of binding of a potential ligand to a  
2 receptor according to claim 2, wherein said neural network is a feed forward network with  
3 back propagation of error that learns with momentum.

1           9. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 4, wherein said neural network is a feed  
3 forward network with back propagation of error that learns with momentum.

1           10. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 5, wherein said neural network is a feed  
3 forward network with back propagation of error that learns with momentum.

1           11. A computer readable medium according to claim 3, wherein said neural  
2 network is a feed forward network with back propagation of error that learns with  
3 momentum.

1           12. A computer readable medium according to claim 6, wherein said neural  
2 network is a feed forward network with back propagation of error that learns with  
3 momentum.

1           13. A method for determining the free energy of binding of a potential ligand to a  
2 receptor according to claim 7, wherein said neural network uses a learning rate between 0.1  
3 and 0.5 and a momentum term between 0.8 and 0.9.

1           14. A method for determining the free energy of binding of a potential ligand to a  
2 receptor according to claim 8, wherein said neural network uses a learning rate between 0.1  
3 and 0.5 and a momentum term between 0.8 and 0.9.

1           15. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 9, wherein said neural network uses a  
3 learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

1           16. A method for determining the free energy of binding of a potential transition-  
2 state inhibitor to a enzyme according to claim 10, wherein said neural network uses a  
3 learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

1           17. A computer readable medium according to claim 11, wherein said neural  
2 network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and  
3 0.9.

1           18. A computer readable medium according to claim 12, wherein said neural  
2 network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and  
3 0.9.